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(71) Applicant *(for all designated States except US)*: RECORDATI S.A. CHEMICAL AND PHARMACEUTICAL COMPANY [CH/CH]; Corso San Gottardo, 54, CH-6830 Chiasso (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TARQUINI, Antonio [IT/IT]; Via Errigo Bernini, 1, I-61029 Urbino (IT). DONNARUMMA, Maria [IT/IT]; Via Montebello, 5, I-04100 Latina (IT).

(74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi S.r.l., Viale Bianca Maria, 33, I-20122 Milano (IT).

(54) Title: A PROCESS FOR PREPARING IOPAMIDOL BY USING A C_1-C_5 MONOALKYLETHER OF A C_2-C_{10} ALKYLENE-GLYCOL

(57) Abstract

A process for purifying iopamidol consisting of crystallizing this product from a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol. This process allows to obtain crystalline iopamidol in a high yield with optimum physical-chemical properties.

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A PROCESS FOR PREPARING IOPAMIDOL BY USING A C_1-C_5 MONOALKYLETHER OF A C_2-C_{10} ALKYLEN-GLYCOL.

FIELD OF THE INVENTION

The present invention relates to a process of purification of iopamidol, by crystallization with a solvent which is a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol.

TECHNOLOGICAL BACKGROUND

(S)-N,N' -bis[2-hydroxy-1-(hydroxy-methyl)ethyl]-2,4,6 -triiodo-5-lactamimido-isophtalimide, commonly known as iopamidol, is a highly soluble non ionic contrast medium, widely utilized in radiology for diagnostic purposes.

USP 4,001,323 describes the synthesis process, starting from 2,4,6-tri-iodo-5-amino-isophtalic acid chloride , which is successively treated with L-2 -acetoxy-propionyl chloride, and finally with 2-amino-1,3 propandiol.

Iopamidol is a white solid, decomposing, without melting at about 300° C, being highly soluble in water, scarcely soluble in methanol and almost insoluble in chloroform and ethanol.

The product as such exhibits a low toxicity, (LD50 ranges from 19,4 in rabbit to 44,5 g/kg in mouse) [The Merck Index 11th Ed. No. 4943 Ed. - Rahway, N.J.USA 1989] however in order to be effective as a contrast medium, it must be administered in quite high dosages.

For example, in the case of i.v. urography, it is suggested administering from 40 to 80 ml of an aqueous solution containing from 61.2 to 75.5% iopamidol [Martindale 13 th Ed., page 708. The

Pharmaceutical Press Ed., London England].

The above high quantities of iopamidol, especially if associated to the potentially critical intravenous administration, render necessary an extreme purification of this product, in order to minimize or avoid any side effect due to the presence of reaction by-products.

For this purpose in US Pharmacopeia it is established that the amount of impurities be not higher than 5000 ppm [US Pharmacopeia Ed. 23, page 828, (1995)].

Iopamidol syntheses described in literature generally contemplate a purification of the final product, starting from its aqueous solution.

For example according to the above mentioned US patent, the product is isolated by evaporation of the aqueous solution thereof and the obtained raw product is crystallized from ethanol.

A similar solution is also encompassed in the International Application WO 88/ 09328, wherein raw iopamidol obtained by evaporation of the aqueous solution is crystallized from anhydrous ethanol, using for the dissolution of iopamidol in this solvent the amount of water still incorporated in iopamidol itself.

These methods utilize the higher solubility in ethanol of the hydrated form than that of the anhydrous form of iopamidol.

In fact it is known that iopamidol can be obtained in hydrated, mono-hydrated or pentahydrated form and in low yields also by slow crystallization from water.

The drawback of these crystallization processes resides in that a significant quantity of solvent, which is not easily removable either by heating at elevated temperatures or under vacuum, always remains in the crystalline product.

Also the remotion of residual traces of water from the crystalline product, coming from the above mentioned crystallization processes, requires prolonged heating at temperatures higher than 100°C.

The most recent GB 2,280,436 describes a process for crystaliizing iopamidol from butanol aqueous solution, allowing to obtain in high yield a crystalline product, having the above mentioned requirements established in US Pharmacopeia.

However this type of purification is practically effective, when the iopamidol to be purified has already a degree of purity very close to that required in Pharmacopeia.

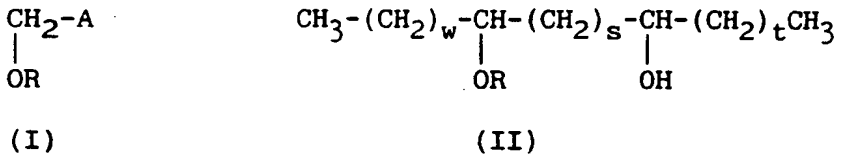
THE PRESENT INVENTION

The Applicant has now unexpectedly found that by using as the crystallization solvent a C_1-C_5 monolakylether of a C_2-C_{10} alkylen- glycol, it is possible to obtain crystalline iopamidol having a purity degree ranging from 99,5 to 99,9 starting from a iopamidol having a HPLC purity degree of 99,1%.

The object of the present invention is a process for obtaining crystalline iopamidol in high yield and in an almost complete absence of residual solvents, comprising crystallizing iopamidol from a a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol as the solvent , optionally in the presence of water.

In particular the C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol

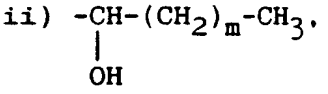
belongs to one of the following classes represented respectively by the following general formulas (I) and (II):

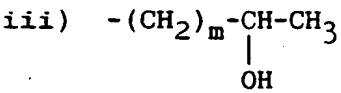


(I) (II)

wherein A has one of the following meanings :

i) $-(CH_2)_l-CH_2-OH$,

ii) 

iii) 

wherein l is = 0 or an integer of from 1 to 8; m is = 0 or an integer of from 1 to 7, in formula (II) w, s and t equal or different from eachother are = 0 or integers of from 1 to 5, provided their sum is not higher than 6, R is a linear or branched alkyl radical of from 1 to 5 carbon atoms .

A further object of the present invention is crystalline iopamidol having a purity degree higher than or equal to 99.5%.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The preferred C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol used in the process according to the present invention are those of formula (I), wherein l or m is preferably = 0 or equal to an integer of from 1 to 3, R is a C_1-C_4 alkyl radical.

According to a particularly preferred embodiment of the process

according to the present invention the C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol is selected from the group consisting of:

1,2 propandiol-monomethylether, 1,2 propandiol-monoethylether, 1,2 propandiol-monobutylether, 1,3 propandiol-monomethylether, 1,3 propandiol-monoethylether, 1,3 propandiol-monobutylether, 2-ethoxyethanol, 2-methoxyethanol.

The process according to the present invention can be carried out in the absence of water, by crystallization of iopamidol from a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol.

In this case for the dissolution of iopamidol in this solvent the amount of water still incorporated in iopamidol itself is used.

The process is preferably carried out in the presence of water.

When the process is carried out in water it preferably comprises the following steps:

a) dissolving iopamidol at a temperature ranging from 80 and 150 °C in a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol and in the presence of the necessary amount of water for solubilizing iopamidol, partially or completely removing water by azeotropic distillation and optionally restoring the distilled solvent;

b) cooling at a temperature comprised between 0 and 90 °C the solution coming from step (a) and recovering the crystallized product by filtration.

The volume of the C_1-C_5 monoalkylether of C_2-C_{10} alkylen- glycol used in step (a) is comprised between 1 and 10 times, preferably between 3 and 5 times the theoretical ponderal quantity of iopamidol

to be purified.

In the same step (a) the following ratio volume of water / volume of solvent is generally comprised between 1/8 and 1/4. In any case the presence of humidity residues in the crystallization mixture does not adversely affect the quality and the yield of the final product, which is in any case obtained in an almost anhydrous form.

Anyway with the process according to the present invention, it is also possible to obtain in high yield the crystallized product in one of the hydrated forms, if in step (a) the water is partially removed.

From an industrial point of view it is preferable to carry out the crystallization directly from an aqueous solution of iopamidol, prepared for this specific purpose or an aqueous solution coming from the same synthesis process. In this case the C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol is preferably added in the above mentioned ratios to the aqueous solution containing iopamidol.

In step (b) the mixture is then heated to carry out the azeotropic distillation of water, and this distillation is continued until the mixture reaches the boiling temperature of the pure solvent.

Small quantities of a third solvent, such as toluene, suitable to form a ternary azeotrope with water, may be added to the mixture of iopamidol water and said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol in order to make easier the complete remotion of water.

The cooling temperature of step (b), in the case the process is carried out in a solvent selected from the group consisting of: 2-ethoxyethanol, 2-methoxyethanol, is preferably comprised between 20 and 90 °C, in the case the process is carried out in the presence of a

solvent selected from the group consisting of: 1,2 propandiol-monomethylether, 1,2 propandiol-monoethylether, 1,2 propandiol-monobutylether, 1,3 propandiol-monomethylether, 1,3 propandiol-monoethylether, 1,3 propandiol-monobutylether, ranges from 0 to 80° C. In both the above mentioned cases the cooling temperature is more preferably comprised between 50 and 70°C.

In step (b) the crystallization of the product occurs, and the product is maintained at the cooling temperature for a period comprised between 30 minutes and 3 hours, the desired product is recovered by filtration and dried under vacuum for 3-4 hours at a temperature of 60° C. The properties of the iopamidol thus obtained are determined by HPLC. For example for determining the HPLC degree of purity of iopamidol the standard operating conditions reported in Pharmeuropa 6, No. 4, page 343 (1994) may be followed . The crystallization yields of the process according to the present invention are very high and in any case are comprised between 80 and 95%.

For illustrative purposes in the following tables reported are the results obtained with the process according to the present invention encompassing in particular the use of a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol , selected from 1-methoxy-2-ethanol, and 1-methoxy-2-propanol in comparison with the corresponding results obtained with the crystallization prior art processes, contemplating the use as crystallization solvents of ethanol, and butanol.

-TABLE 1-

Solvent	HPLC Starting purity (%)	Yield (%)	HPLC Final purity (%)
ethanol	99.1	95	99.2
n-butanol	99.1	97	99.3
1-methoxy--2-ethanol	99.1	88	99.7
1-methoxy--2-propanol	99.1	89	99.6

The following examples are reported of the process according to the present invention for illustrative, but not limitative purposes .

EXAMPLE 1

10 g iopamidol (12,8 mmol) with HPLC purity degree 99,1% are suspended in 40 ml 2-methoxyethanol (Methyl-Cellosolve ^{R}) and 5 ml water are added to the suspension.

The mixture is then heated under reflux (104-105°C), until complete dissolution of the suspension. 45 ml solvent consisting of an azeotropic mixture of water and 2-methoxyethanol are then removed by distillation. The starting volume is restored by adding 2-methoxyethanol and the obtained mixture is cooled to 70°C. The precipitated solid is then recovered by filtration and dried under vacuum at 60° C. 8,8 g of iopamidol are obtained (yield 88%) with

HPLC purity degree 99,7%.

EXAMPLE 2

10 g iopamidol (12,8 mmol) with HPLC purity degree 99,1% are treated with 40 ml 2-methoxyethanol and 5 ml water, by following the same operating conditions of Example 1. After azeotropic distillation and restoration of the starting volume of the solvent, the mixture is cooled to 25° C. A solid precipitates, which is recovered by filtration, then it is dried under vacuum at 60° C to give 9 g iopamidol (yield 90%) with HPLC purity degree 99.5%.

EXAMPLE 3

10 g iopamidol (12,8 mmol) with HPLC purity degree 99,1% are suspended in 40 ml 2-ethoxyethanol (Cellosolve^{R}), and 5 ml water are added to the suspension thus obtained.

The mixture is then heated under reflux (104-105° C), until complete dissolution of the suspension. 45 ml solvent consisting of an azeotropic mixture of water and 2-ethoxyethanol are then removed by distillation. The starting volume is restored by adding 2-ethoxyethanol and the obtained mixture is cooled to 70° C. The precipitated solid is then recovered by filtration and dried under vacuum at 60° C. 8,8 g of iopamidol are obtained (yield 88%) with HPLC purity degree 99,7%.

EXAMPLE 4

10 g iopamidol (12,8 mmol) with HPLC purity degree 99.1% are suspended in 40 ml 1-methoxy-2-propanol and 5 ml water are added to the suspension thus obtained. The mixture is heated to the reflux temperature of the solvent (110-115° C), until complete dissolution of

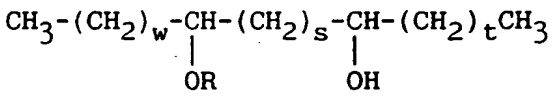
the suspension. The azeotropic distillation is then carried out until the temperature of the vapours reaches 118° C. The starting volume of 1-methoxy-propanol is then restored, while maintaining the temperature of the mixture comprised between 110 and 115° C. The mixture is then cooled to 70° C and left at this temperature for 2 hours. The precipitated solid is filtered at 70°C and dried under vacuum at 60°C. 8.9 g iopamidol are obtained (yield 89%), having HPLC purity degree 99.6%.

CLAIMS

1. A process for obtaining crystalline iopamidol in a high yield in almost complete absence of residual solvents comprising crystallizing said product from a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol, as the solvent.

2. The process according to claim 1, wherein said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol belongs to one of the following classes represented respectively by the following general formulas (I) and (II):

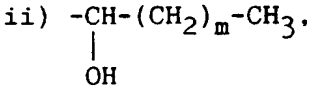
(I)

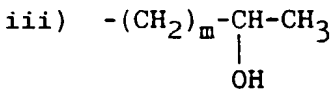


(II)

wherein A has one of the following meanings :

i) $-(CH_2)_l-CH_2-OH$.

ii) 

iii) 

wherein l is = 0 or an integer of from 1 to 8; m is = 0 or an integer of from 1 to 7, in formula (II) w, s and t equal or different from eachother are = 0 or integers of from 1 to 5, provided their sum is not higher than 6, R is a linear or branched alkyl radical of from 1 to 5 carbon atoms.

3. The process according to claim 2, wherein, a C_1-C_5 monoalkylether

of a C_2-C_{10} alkylen- glycol of formula (I) is used as the solvent, having 1 or m = 0 or equal to an integer of from 1 to 3, R is a C_1-C_4 alkyl radical.

4. The process according to claim 3, wherein the C_1-C_5 monoalkylether of a C_2-C_{10} alkylen- glycol is selected from the group consisting of: 1,2 propandiol-monomethylether, 1,2 propandiol-monoethylether, 1,2 propandiol-monobutylether, 1,3 propandiol-monomethylether, 1,3 propandiol-monoethylether, 1,3 propandiol-monobutylether, 2-ethoxyethanol, 2-methoxyethanol.

5. The process according to claim 1, wherein the iopamidol is crystallized from said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol in the absence of water.

6. The process according to claim 1, wherein it is carried out in the presence of water and comprises the following steps:

a) dissolving iopamidol at a temperature ranging from 80 to 150 °C in a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol and in the presence of the amount of the necessary water for solubilizing iopamidol, partially or completely removing water by azeotropic distillation and optionally restoring the distilled solvent;

b) cooling at a temperature comprised between 0 and 90 °C the solution coming from step (a) and recovering the crystallized product by filtration.

7. The process according to claim 6, wherein in step (a) said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol is added to an aqueous solution containing iopamidol prepared for this purpose, or an aqueous

solution coming from the synthesis process of iopamidol itself.

8. The process according to claim 6 , wherein in step (a) the volume of said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol is comprised between 1 and 10 times the theoretical ponderal amount of iopamidol to be purified, and the following ratio volume of water / volume of said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol is comprised between 1/8 and 1/4.

9. The process according to claim 8, wherein the volume of said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol is comprised between 3 and 5 times the theoretical ponderal amount of iopamidol to be purified.

10. The process according to claim 6, wherein, when in step (a) the water is partially removed, one of the hydrated forms is obtained of iopamidol.

11. The process according to claim 6, wherein in step (a) a third solvent is used, able to form a ternary azeotrope with water and said C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol.

12. The process according to claim 6, wherein the cooling temperature of step (b), when the process is carried out in a solvent selected from the group consisting of: 2-ethoxyethanol, 2-methoxyethanol is comprised between 20 and 90° C, when the process is carried out in the presence of a solvent selected from the group consisting of: 1,2 propandiol-monomethylether, 1,2 propandiol-monoethylether, 1,2 propandiol-monobutylether, 1,3 propandiol-monomethylether, 1,3 propandiol-monoethylether, 1,3 propandiol-monobutylether, it ranges from 0 to 80° C.

13. The process according to claim 12 wherein the cooling temperature

of step (b) is comprised between 50 and 70° C.

14. The process according to claim 6 , wherein in step (b) the product is maintained at the cooling temperature for a period comprised between 30 minutes and 3 hours, then the desired product is recovered by filtration and dried under vacuum for 3-4 hours at a temperature of 60° C.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/02863

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C227/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,2 280 436 (ZAMBON SPA) 1 February 1995 cited in the application see claims	1-14
A	WO,A,88 09328 (BRACCO IND CHIMICA SPA) 1 December 1988 cited in the application see page 26 - page 28; claims	1-14
A	ANAL. PROFILES DRUG SUBST. (1988), 17, 115-54 CODEN: APDSB7;ISSN: 0099-5428, XP002012662 FELDER, ERNST ET AL: "Iopamidol" see page 132 - page 135	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Sánchez García, J.M.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	2128942	31-01-95
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(71) Applicant *(for all designated States except US)*: RECORDATI S.A. CHEMICAL AND PHARMACEUTICAL COMPANY [CH/CH]; Corso San Gottardo, 54, CH-6830 Chiasso (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TARQUINI, Antonio [IT/IT]; Via Errigo Bernini, 1, I-61029 Urbino (IT). DONNARUMMA, Maria [IT/IT]; Via Montebello, 5, I-04100 Latina (IT).

(74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi S.r.l., Viale Bianca Maria, 33, I-20122 Milano (IT).

(54) Title: A PROCESS FOR PREPARING IOPAMIDOL BY USING A C_1-C_5 MONOALKYLETHER OF A C_2-C_{10} ALKYLEN-GLYCOL

(57) Abstract

A process for purifying iopamidol consisting of crystallizing this product from a C_1-C_5 monoalkylether of a C_2-C_{10} alkylen-glycol. This process allows to obtain crystalline iopamidol in a high yield with optimum physical-chemical properties.

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